Physical activity and stroke. A meta-analysis of observational data

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Physical activity and stroke. A meta-analysis of observational data

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Background Based on studies published so far, the protective effect of physical activity on stroke remains controversial. Specifically, there is a lack of insight into the sources of heterogeneity between studies.

Methods Meta-analysis of observational studies was used to quantify the relationship between physical activity and stroke and to explore sources of heterogeneity. In total, 31 relevant publications were included. Risk estimates and study characteristics were extracted from original studies and converted to a standard format for use in a central database.

Results Moderately intense physical activity compared with inactivity, showed a protective effect on total stroke for both occupational (RR = 0.64, 95% CI: 0.48–0.87) and leisure time physical activity (RR = 0.85, 95% CI: 0.78–0.93). High level occupational physical activity protected against ischaemic stroke compared with both moderate (RR = 0.77, 95% CI: 0.60–0.98) and inactive occupational levels (RR = 0.57, 95% CI: 0.43–0.77). High level compared with low level leisure time physical activity protected against total stroke (RR = 0.78, 95% CI: 0.71–0.85), haemorrhagic stroke (RR = 0.74, 95% CI: 0.57–0.96) as well as ischaemic stroke (RR = 0.79, 95% CI: 0.69–0.91). Studies conducted in Europe showed a stronger protective effect (RR = 0.47, 95% CI: 0.33–0.66) than studies conducted in the US (RR = 0.82, 95% CI: 0.75–0.90).

Conclusions Lack of physical activity is a modifiable risk factor for both total stroke and stroke subtypes. Moderately intense physical activity is sufficient to achieve risk reduction.

Keywords Physical activity, stroke, haemorrhagic, ischaemic, meta-analysis, heterogeneity

It has been well established that physical activity plays an important role in preventing coronary heart disease and cardiovascular diseases in general.[1–3] In 1999, Wannamethee and Shaper published a review, including five cohort studies, addressing the relationship between physical activity and stroke. They concluded that most of these studies had shown physical activity to be associated with a reduced risk of stroke and that moderate levels of physical activity may be sufficient to achieve a significant reduction in stroke risk.[4] However, no effort was made to present pooled risk estimates and to explain discrepant results of studies included in the review. Therefore, in the present meta-analysis we not only aimed to calculate pooled risk estimates. We specifically aimed to explore sources of heterogeneity that may have influenced the observed relationships between physical activity and stroke. Pooled risk estimates were calculated for total stroke, haemorrhagic stroke and ischaemic stroke, stratified by type of activity.

Methods

Data sources

The PUBMED database was searched for studies published in English until December 2001. We used various combinations of the keywords physical activity, exercise, cerebrovascular disease, stroke, ischaemic stroke, and haemorrhagic stroke. References from the publications obtained were searched for more references, new publications retrieved and again searched

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for more references. This process was repeated until no additional references could be identified. We reviewed all relevant papers and identified 36 published cohort or case-control studies on physical activity and stroke.

Study selection

Studies in which physical fitness was used as an estimate for physical activity were not considered eligible because physical fitness or aerobic power is a proxy measure for vigorous activity and not for physical activity in general.[3] Consequently, one study was excluded from the analysis.[5]

For some cohort studies, multiple publications were found.[6–13] As a rule, the publication with the longest follow-up time was included in the meta-analysis, resulting in exclusion of four studies.[6,8,10,12] Eventually, 31 relevant publications (24 cohort and 7 case-control studies) were included in the meta-analysis.[7,9,11,13–40]

Data extraction

Risk estimates and study characteristics were extracted from original studies, double-checked and converted to a standard format for use in a central database. Risk estimates and the accompanying standard errors were extracted from the publications and converted to a log-scale for use in the meta-regression analysis. If *P*-values were reported as for example <0.05, we assumed a *P*-value of 0.05 in order to be able to calculate a maximum standard error. In some cases no *P*-value, standard error or CI could be extracted from the publication. If possible, the authors of the particular publications were contacted and asked to provide us with the necessary information. Finally, part of the information was missing regarding two publications.[27,28] Some studies reported risk estimates for different subgroups of their population (e.g. gender or age). These subgroups were included in the meta-analysis as separate data units. Consequently, the 'N' column in Tables 3, 4, and 5 represents data units and not publications.

In order to assess the extent of publication bias in this meta-analysis, we constructed funnel plots for total, haemorrhagic, and ischaemic stroke by plotting the natural logarithm of the effect measure against the inverse of the standard error of this measure. A deficit of negative imprecise studies in these funnel plots was assumed to indicate publication bias. In addition, we used Egger's method to test asymmetry in our funnel plots.[41] Publication bias was assumed to be present if, at $P < 0.1$, the intercept significantly differed from zero.

Meta-regression analysis was performed as described by van Houwelingen *et al*. with use of the standard Wald CI.[42] We performed a test of heterogeneity in order to decide between meta-regression analysis using a fixed-effects (no significant inter-study variation) or a random-effects approach (significant inter-study variation). Because of the small number of studies in the various strata, we chose a conservative approach and assumed heterogeneity up to a two-sided *P*-value of 0.5. In addition, we calculated the I^2 statistic for all random effect models as suggested by Higgins and Thompson.[43] This statistic can be interpreted as the proportion of total variation in study estimates that is due to heterogeneity. In contrast to the χ^2 statistic for heterogeneity, this statistic is not dependent on the number of studies in the meta-analysis.[43]

Stratified analyses were used to ensure that studies within strata would be similar in both outcome and physical activity measure. First, we stratified for type of physical activity (occupational and leisure time physical activity). Because occupational and leisure time physical activity may include different levels of physical activity and therefore could have different physiological effects, we chose to separate these two general types of activity. Studies that reported on an integrated physical activity level of both occupational and leisure time physical activity (n = 3) were grouped with the studies reporting only on leisure time physical activity.

Within the strata for type of physical activity, further stratification was made for four combinations of reference and comparison categories: (A) active versus inactive for studies that present risk estimates for more than two activity categories; (B) active versus moderately active for studies that present risk estimates for more than two activity categories; (C) moderately active versus inactive for studies that present risk estimates for more than two activity categories, and (D) active versus inactive for studies that present risk estimates for dichotomized activity categories. These separate analyses can be seen as an estimation of a dose–response relation between activity level and risk for stroke.[1] As a rule for this meta-analysis, the lowest category was defined as inactive, the highest as active. All categories in between were pooled to represent a moderately active category.

A third stratification was made for the outcome measure. The aetiology of ischaemic stroke differs from the aetiology of haemorrhagic stroke.[44,45] Therefore, it may be possible that the mechanism by which physical activity affects ischaemic and haemorrhagic stroke differs. Consequently, we will provide separate summary risk estimates for ischaemic and haemorrhagic stroke. Because some studies did not report separate risk estimates for these subtypes of stroke, we also calculated a summary risk estimate for total stroke.

In addition to calculating pooled effect measures for different strata of physical activity and stroke, we performed meta-regression analysis to explore the influence of several factors on the pooled effect measure. Because of the generally small number of studies per stratum addressing occupational physical activity, these analyses were restricted to studies on leisure time physical activity. For the same reason analyses were further limited to studies in stratum A, e.g. active versus inactive for studies that present risk estimates for more than two activity categories.

The influence of study quality was investigated by calculating a pooled risk estimate weighted for this study characteristic. Study quality was determined using an adapted version of the scoring system proposed by Powell *et al*. and previously used by Berlin and Colditz.[1,2] The scoring system included three main aspects of study design: measurement of physical activity, measurement of disease status, and epidemiological methods (Appendix). Each component was rated according to its presence (no or uncertain, partly present, yes) in the individual studies. These ratings were coded as 0, 1, and 2, resulting in a total score (e.g. the sum of all sub-ratings) with a possible range from 0 to 32. The adaptation we made to the score concerned one of the characteristics of measurement of disease status. Powell *et al*. included an item on the diagnosis of coronary heart disease, whereas in the present meta-analyses an item on the diagnosis of stroke subtypes was admitted. We defined that

Table 1 Case-control studies on occupational or leisure time physical activity included in the present meta-analysis.

First author	Year	Country	Study size	Outcome type	Cases	Relative risk	Quality score
Occupational physical activity							
—		—		—		—	—
Leisure time physical activity							
Herman[36]	1983	Europe	371 men and women	Total stroke	132	A versus I: 0.24 (0.10, 0.59) M versus I: 0.49 (0.31, 0.77)	22
Shinton[38]	1993	Europe	171 men 152 women	Total stroke	73 52	A versus I: 0.30 (0.1, 0.6) A versus I: 0.37 (0.2, 0.8)	23
You[34]	1995	US	406 men and women	Ischaemic stroke	203	A versus I: 0.3 (0.1, 0.7) M versus I: 1.0 (0.4, 2.3)	27
You[40]	1997	Australia	402 men and women	Ischaemic stroke	201	A versus I: 0.6 (0.3, 1.3) M versus I: 1.4 (0.6, 3.3)	22
Sacco[37]	1998	US	1047 men and women	Ischaemic stroke	369	A versus I: 0.23 (0.10, 0.54) M versus I: 0.39 (0.26, 0.58)	26
Fann[35]	2000	US	447 men and women	Haemorrhagic stroke	149	A versus I: 0.7 (0.4, 1.1) M versus I: 0.8 (0.4, 1.3)	17
Thrift[39]	2002	Australia	396 men	Haemorrhagic stroke	198	A versus I: 0.57 (0.28, 1.14) M versus I: 0.57 (0.26, 1.23)	27
			266 women		133	A versus I: 1.26 (0.43, 3.70) M versus I: 0.57 (0.11, 2.99)	

diagnoses of stroke should preferably be made separately for ischaemic and haemorrhagic stroke (Appendix).

For the present meta-analysis, the various components were scored separately by three people (GW, AS, and EF) using blinded versions of the publication (e.g. without source, title, authors, results, discussion, and references). If the scores given did not agree (5 out of 28 publications), consensus on a score was reached by discussion.

The influence of type of study design, gender of the study population, country under study, and year of publication was investigated by adjusting the meta-regression model for these variables. Dummy variables were created for type of study, gender of the study population, and country under study. Year of publication was added to the model as continuous variable. These analyses were restricted to studies that reported separate risk estimates for men and women, excluding three studies on total stroke, one study on haemorrhagic stroke, and three studies on ischaemic stroke.

Results

The characteristics and estimated effect measures of the 31 retrieved cohort and case-control studies are chronologically summarized in Table 1 (case-control studies), Table 2a (cohort studies on occupational physical activity), and Table 2b (cohort studies on leisure time physical activity). Case-control studies did not report on occupational physical activity (Table 1). Among cohort studies, a clear shift over time was noted for the type of physical activity under study. Older publications more frequently reported on occupational activity, whereas more recent publications tended to report on leisure time physical activity (Table 2a and Table 2b). Approximately 70% of the case-control studies and 50% of the cohort studies reported an effect measure for either or both ischaemic and haemorrhagic stroke (Table1, Table 2a, and Table 2b). Generally, recent publications more often reported on subtypes of stroke. Case-control studies generally failed to report an odds ratio separately for men and women (Table 1), whereas more than 75% of the cohort studies did report an effect measure for men and women separately (Table 2a and Table 2b). The quality score of case-control studies was generally higher than the quality score of cohort studies (Table 1, Table 2a, and Table 2b). Among cohort studies, the quality score of more recent studies tended to be higher than the score of earlier studies (Table 2a and Table 2b).

Funnel plots and Egger's test for asymmetry generally showed that publication bias in the present meta-analysis was limited (Figure 1). The results for ischaemic stroke were however borderline significant ($P = 0.1$; Figure 1)

Table 3 (occupational physical activity) and Table 4 (leisure time physical activity) present the results for three stroke outcomes (total, haemorrhagic, and ischaemic), stratified by the combination of reference and comparison groups of physical activity. In general, physical activity protected against stroke. People who were active at work were at lower risk of ischaemic stroke compared with both inactive (RR = 0.57, 95% CI: 0.43, 0.77) and moderately active (RR = 0.77, 95% CI: 0.60, 0.98) people at the workplace. In turn, moderately active people at the workplace were at lower risk of total stroke (RR = 0.64, 95% CI: 0.48, 0.87) compared with people who were inactive at the workplace (Table 3). People who were active during leisure time were at lower risk of total stroke (RR = 0.78, 95% CI: 0.71, 0.85), haemorrhagic stroke (RR = 0.74, 95% CI: 0.57, 0.96) as well as ischaemic stroke (RR = 0.79, 95% CI: 0.69, 0.91), compared with those who were inactive during leisure time (Table 4). In addition, people who were moderately active during leisure time were at lower risk of total stroke (RR = 0.85, 95% CI: 0.78, 0.93) compared with inactive people (Table 4).

Results of the analyses conducted in order to study sources of heterogeneity are shown in Table 5. Analyses weighted for the quality score did not meaningfully change the risk estimate, but

Table 2a Cohort studies on occupational physical activity included in the present meta-analysis

First author	Year	Country	Study size	Outcome type	Cases	Relative risk	Quality score
Okada[28]	1976	Japan	4186 men and women	Haemorrhagic stroke	143	A versus M: 0.79 (…, …)[a] A versus I: 0.31 (0.13, 0.76)	19
				Ischaemic stroke	109	A versus M: 0.44 (…, …)[a] A versus I: 0.44 (…, …)[a]	
Paffenbarger[9]	1978	US	3686 men	Total stroke	112	A versus I: 0.62 (0.34, 1.14)	17
				Haemorrhagic stroke	60	A versus I: 0.58 (0.2, 1.34)	
				Ischaemic stroke	52	A versus I: 0.67 (0.27, 1.67)	
Salonen[30]	1982	Europe	3978 men	Total stroke	71	A versus I: 0.63 (0.40, 0.91)	18
			3688 women		56	A versus I: 0.59 (0.37, 0.91)	
Menotti[26]	1985	Europe	99 029 men	Total stroke	187	A versus I: 1.00 (0.75, 1.35)	15
						M versus I: 0.65 (0.45, 0.93)	
						A versus M: 1.53 (1.08,2.16)	
Lapidus[22]	1986	Europe	1351 women	Total stroke	13	A versus I: 7.8 (2.7, 23.0)	21
Harmsen[20]	1990	Europe	7495 men	Total stroke	148	A versus I: 0.91 (0.67, 1.43)	21
				Haemorrhagic stroke	31	A versus I: 0.75 (0.00, 2.07)	
				Ischaemic stroke	69	A versus I: 1.11 (0.67, 1.67)	
Menotti[7]	1990	US and Europe	8287 men	Total stroke	353	A versus I: 0.99 (0.86, 1.14)	15
Haheim[19]	1993	Europe	14 403 men	Total stroke	81	A versus I: 1.62 (0.95, 2.75) M versus I: 0.66 (0.34, 1.23)	19
Gillum[18]	1996	US	2713 men	Total stroke	69 aged 45–64	A versus M: 0.57 (0.34, 0.96) A versus I: 0.93 (0.35, 2.50)	23
					201 aged 65–74	A versus M: 0.83 (0.61, 1.14) A versus I: 0.55 (0.35, 0.87)	
				Ischaemic stroke	60 aged 45–64	A versus M: 0.54 (0.31, 0.95) A versus I: 0.76 (0.28, 2.04)	
					186 aged 65–74	A versus M: 0.85 (0.62, 1.19) A versus I: 0.59 (0.36, 0.95)	
			2368 women	Total stroke	53 aged 45–64	A versus M: 0.93 (0.50, 1.75) A versus I: 0.28 (0.13, 0.60)	
					196 aged 65–74	A versus M: 0.70 (0.50, 0.99) A versus I: 0.55 (0.33, 0.91)	
				Ischaemic stroke	48 aged 45–64	A versus M: 0.85 (0.43, 1.64) A versus I: 0.22 (0.10, 0.49)	
					179 aged 65–74	A versus M: 0.70 (0.49, 1.00) A versus I: 0.57 (0.34, 0.98)	
Nakayama[27]	1997	Japan	961 men	Total stroke	64	A versus M: 1.88 (0.72, 4.88) M versus I: 0.72 (0.40, 1.30)	22
				Haemorrhagic stroke	8	A versus M: 3.36 (0.36, 31.57) M versus I: 0.72 (0.14, 3.70)	
				Ischaemic stroke	37	A versus M: 2.09 (0.61, 7.19) M versus I: 0.90 (0.42, 1.92)	
			1341 women	Total stroke	78	A versus M: …. (…, …)[b] M versus I: 0.54 (0.30, 0.97)	
				Haemorrhagic stoke	19	A versus M: …. (…, …)[b] M versus I: 0.35 (0.11, 1.14)	
				Ischaemic stroke	39	A versus M: …. (…, …)[b] M versus I: 0.48 (0.20, 1.12)	
Evenson[17]	1999	US	14 575 men and women	Ischaemic stroke	189	A versus I: 0.69 (0.46, 1.02) M versus I: 0.59 (0.03, 1.14)	27

[a] No *P*-value or CI was reported.

[b] Not reported in the original paper due to biased distribution of variables or small number of events.

Table 2b Cohort studies on leisure time physical activity included in the present meta-analysis[a]

First author	Year	Country	Study size	Outcome type	Cases	Relative risk	Quality score
Salonen[30]	1982	Europe	3978 men	Total stroke	71	A versus I: 1.00 (0.67, 1.43)	18
			3688 women		56	A versus I: 0.77 (0.50, 1.25)	
Lapidus[22]	1986	Europe	1351 women	Total stroke	13	A versus I: 10.1 (3.8, 27.1)	21
Folsom[32]	1990	US	41 837 women	Total stroke	218	A versus I: 0.6 (0.4, 0.9) M versus I: 0.8 (0.5, 1.1)	9
Harmsen[20]	1990	Europe	7495 men	Total stroke	148	A versus I: 0.83 (0.56, 1.25)	21
				Haemorrhagic stroke	31	A versus I: 0.77 (0.00, 2.18)	
				Ischaemic stroke	69	A versus I: 0.83 (0.50, 1.43)	
Lindsted[25]	1991	US	9484 men	Total stroke	410	A versus I: 0.94 (0.65, 1.36) M versus I: 0.78 (0.61, 1.00)	18
Wannamethee[31]	1992	Europe	7735 men	Total stroke	128	A versus I: 0.20 (0.10, 0.90) M versus I: 0.65 (0.00, 1.37)	21
Haheim[19]	1993	Europe	14 403 men	Total stroke	81	A versus I: 0.36 (0.15, 0.80) M versus I: 0.64 (0.38, 1.08)	19
Lindenstrom[24]	1993	Europe	7060 women	Total stroke	265	A versus I: 1.45 (1.01, 2.08)	17
Simonsick[33]	1993	US	5177 men and women	Total stroke	161	A versus I: 0.86 (0.06, 1.67) M versus I: 1.25 (0.64, 1.86)	17
Abbott[14]	1994	Asia	7530 men	Haemorrhagic stroke	62 aged 45–54	A versus I: 0.5 (0.2–1.3) M versus I: 0.9 (0.3, 2.5)	24
					67 aged 55–68	A versus I: 0.3 (0.1, 0.8) M versus I: 0.5 (0.2, 1.3)	
Kiely[13]	1994	US	1897 men	Total stroke	188	A versus I: 0.84 (0.59, 1.18) M versus I: 0.90 (0.62, 1.31)	18
			2299 women		214	A versus I: 0.89 (0.60, 1.31) M versus I: 1.21 (0.89, 1.63)	
Gillum[18]	1996	US	2713 men	Total stroke	69 aged 45–64	A versus M: 0.85 (0.44, 1.64) A versus I: 0.81 (0.41, 1.59)	23
					201 aged 65–74	A versus M: 1.16 (0.78–1.72) A versus I: 0.78 (0.53, 1.14)	
				Ischaemic stroke	60 aged 45–64	A versus M: 0.86 (0.43, 1.72) A versus I: 0.91 (0.45, 1.85)	
					186 aged 65–74	A versus M: 1.12 (0.74, 1.69) A versus I: 0.75 (0.50, 1.11)	
			2368 women	Total stroke	53 aged 45–64	A versus M: 0.56 (0.16, 1.92) A versus I: 0.32 (0.10, 1.05)	
					196 aged 65–74	A versus M: 0.79 (0.47, 1.32) A versus I: 0.65 (0.40, 1.05)	
				Ischaemic stroke	48 aged 45–64	A versus M: 0.65 (0.18, 2.27) A versus I: 0.35 (0.10, 1.15)	
					179 aged 65–74	A versus M: 0.81 (0.48, 1.39) A versus I: 0.68 (0.41, 1.14)	
Lee[11]	1998	US	11 130 men	Total stroke	378	A versus I: 0.82 (0.58, 1.14) M versus I: 0.69 (0.30, 1.09)	21
Lee[23]	1999	US	21 823 men	Total stroke	533	A versus I: 0.86 (0.65, 1.13) M versus I: 0.86 (0.56, 1.15)	26
				Haemorrhagic stroke	84	A versus I: 0.54 (0.26, 1.15) M versus I: 0.65 (0.00, 1.40)	
				Ischaemic stroke	437	A versus I: 0.97 (0.71, 1.32) M versus I: 0.93 (0.61, 1.26)	
Evenson[17]	1999	US	14 575 men and women	Ischaemic stroke	189	A versus I: 0.82 (0.51, 1.32) M versus I: 0.77 (0.30, 1.24)	27

Table 2b Continued

First author	Year	Country	Study size	Outcome type	Cases	Relative risk	Quality score
Agnarsson[15]	1999	Europe	4484 men	Total stroke	249	A versus I: 0.69 (0.47, 1.01)	22
				Ischaemic stroke	158	A versus I: 0.62 (0.40, 0.97)	
Hu[21]	2000	US	72 488 women	Total stroke	407	A versus I: 0.66 (0.47, 0.91) M versus I: 0.87 (0.52, 1.21)	27
				Haemorrhagic stroke	109	A versus I: 1.02 (0.58, 1.82) M versus I: 0.85 (0.15, 1.55)	
				Ischaemic stroke	258	A versus I: 0.52 (0.33, 0.80) M versus I: 0.83 (0.40, 1.25)	
Ellekjaer[16]	2000	Europe	14 101 women	Total stroke	457	A versus I: 0.52 (0.38, 0.72) M versus I: 0.77 (0.61, 0.98)	22
Paganini-Hill[29]	2001	US	4722 men	Total stroke	773	A versus I: 0.85 (0.72, 1.01) M versus I: 0.91 (0.76, 1.10)	16
				Haemorrhagic stroke	69	A versus I: 0.69 (0.38, 1.25) M versus I: 1.06 (0.59, 1.92)	
				Ischaemic stroke	351	A versus I: 0.96 (0.74, 1.24) M versus I: 1.04 (0.79, 1.39)	
			8532 women	Total stroke	1211	A versus I: 0.83 (0.73, 0.95) M versus I: 0.88 (0.76, 1.01)	
				Haemorrhagic stroke	105	A versus I: 1.00 (0.64, 1.56) M versus I: 0.71 (0.42, 1.20)	
				Ischaemic stroke	508	A versus I: 0.81 (0.66, 1.00) M versus I: 0.95 (0.76, 1.18)	

[a] Including studies on an integrated measure for physical activity base on both occupational and leisure time physical activity.

did tend to narrow the 95% CI (Table 5). The type of study design and the year of publication did not significantly contribute to the statistical explanation of the pooled risk estimate. A borderline significant effect ($P = 0.07$) was found for the gender of the study population among studies on haemorrhagic stroke. In male populations, being active during leisure time was associated with a 0.54 (95% CI: 0.36, 0.81) risk of haemorrhagic stroke compared with being inactive during leisure time. In female populations, this risk was 0.76 (95% CI: 0.67, 0.86; Table 5). For total stroke, a significant effect ($P = 0.008$) was found for the country under study (either US or Europe). Among studies conducted in Europe, the pooled risk estimate for being active during leisure time was 0.47 (95% CI: 0.33, 0.66) compared with being inactive during leisure time, for studies conducted in the US this risk estimate was 0.82 (95% CI: 0.75, 0.90; Table 5).

Discussion

The results of this meta-analysis indicate an association between physical activity and a lower risk of stroke. For occupational physical activity, being active was associated with a 43% and 23% lower risk of ischaemic stroke compared with respectively being inactive and being moderately active. Being moderately active at work was associated with a 36% lower risk of total stroke compared with being inactive at work. For leisure time physical activity, being active was associated with a 20–25% lower risk compared with being inactive. Being moderately active during leisure time was associated with a 15% lower risk on total stroke compared with being inactive during leisure time. Gender was a borderline and country under study was a clear source of heterogeneity among studies on leisure time physical activity and stroke risk.

As in all meta-analyses, we need to address publication bias. Based on funnel-plots and accompanying Egger tests, publication bias in the present meta-analysis seemed to be limited, although it could not be excluded. Only for ischaemic stroke we detected possible publication bias (e.g. borderline significance in the Egger test). Therefore, the pooled risk estimate for ischaemic stroke may be, to a small extent, biased. By restricting our search of the literature to English language papers we potentially introduced language bias into the meta-analysis. In 1997, Egger *et al*. published a study on language bias in randomized controlled trials and they concluded that the only study characteristic that predicted publication in an English language journal was a significant result reported in the original study.[46] Therefore, if in the present meta-analysis language bias would have been present, this would probably have been reflected in our test for publication bias. Since publication bias was limited, language bias probably was limited too.

One limitation of our meta-analysis is that relatively few case-control studies were available, resulting in low power for testing the effect of study design on the pooled risk estimate. Within our analyses on sources of heterogeneity, only two case-control studies were available. Both studies were focussed on haemorrhagic stroke and the dummy variable for type of study was far from statistically significant ($P = 0.9$). Therefore, we were not able to properly test the influence of study design on the pooled risk estimate.

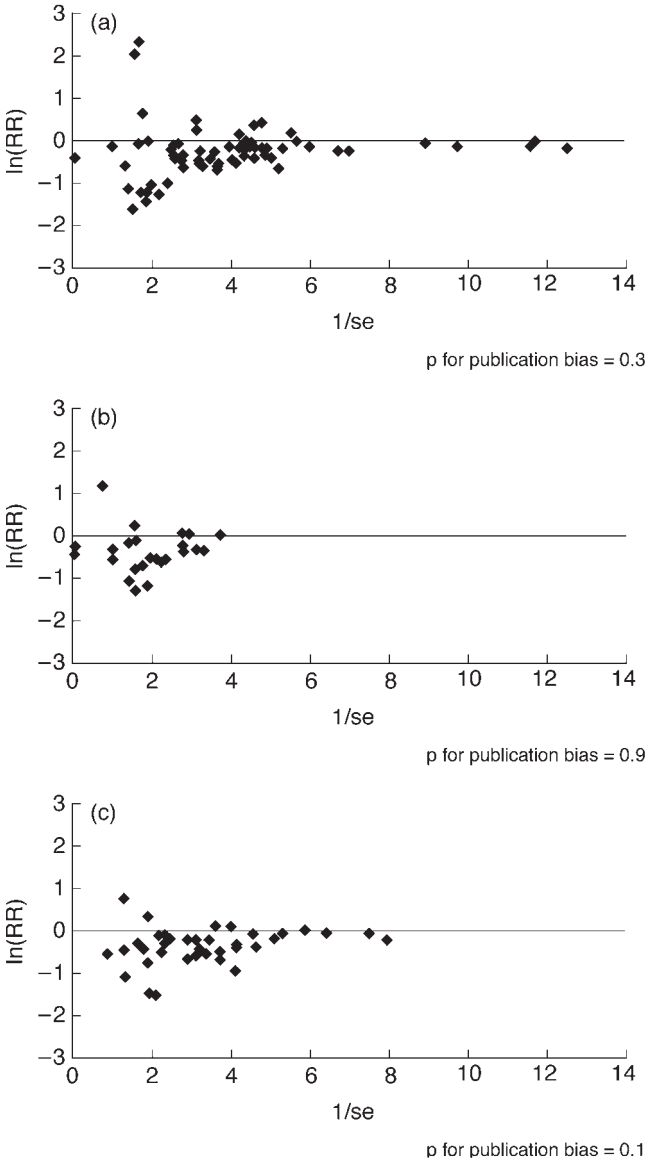

Figure 1 Funnel plots for total stroke (a), hemorrhagic stroke (b), and ischemic stroke (c)

In addition, pooled risk estimates from fixed meta-regression models showed wider 95% CI for occupational physical activity than for leisure time physical activity. Probably, this was a result of the relatively few studies that were available on occupational physical activity and stroke risk. This likely contributed to the relatively high proportion of total variation in study estimates due to heterogeneity (I^2, calculated for the random effect meta-regression models) among studies on occupational physical activity. Consequently, results on leisure time physical activity generally seemed to be more reliable than results on occupational physical activity. Therefore, more studies on occupational physical activity and stroke risk are needed to conclude whether or not this is a statistical artifact or a genuine characteristic of these studies.

Another limitation is the relatively small amount of studies addressing the relation between physical activity and haemorrhagic stroke, especially for occupational physical activity. More studies are needed to be able to make reliable quantitative statements about the relation of physical activity to haemorrhagic stroke.

We assumed that active participants were comparable among studies, as well as inactive and moderately active participants. This is probably not true, since the definitions of high, moderate, and low levels of physical activity varied substantially among studies. This will have caused the contrasts between active and inactive physical activity categories to level off when calculating pooled risk estimates. Therefore, it is likely that the pooled risk estimates presented in the present meta-analysis give an underestimation of the true relationship of physical activity to stroke occurrence. Consequently, this phenomenon may be the explanation for the lack of significance of pooled risk estimates and high heterogeneity in results for studies that reported dichotomized activity categories. The variability in the definition of physical activity categories also makes it impossible to quantify the specific amount and intensity of physical activity needed to prevent stroke.

In the present meta-analysis also the degree of adjustment for confounding variables varied from study to study. Some studies presented risk estimates adjusted for only age and others included a wide variety of risk factors for stroke. In addition, by performing a meta-analysis we were limited in adjusting the pooled risk estimate for confounders that were reported in the original papers. Therefore, the pooled risk estimates calculated in the present meta-analysis will include some confounding of the true relationship between physical activity and stroke occurrence.

Overall, our meta-analysis was limited by the small number of data units within strata. This lead to a lack of power for conducting analyses to study sources of heterogeneity. We explored study quality, type of study design, gender of the study population, country under study, and year of publication as sources of heterogeneity that could have influenced the results of separate studies. With the exception of the (borderline) significant effect of gender and country, none of these factors significantly contributed to the pooled risk estimate. Other interesting features would have been the average age of the population and adjustment for risk factors in individual studies. In the future, when more studies on the relationship between physical activity and stroke have been published, it might be possible to take these factors into account.

In the present meta-analysis, country under study was identified as a significant source of heterogeneity among studies on leisure time physical activity and total stroke. From the 16 data units included in this analysis, 13 came from 8 different American studies, the other 3 came from three different European studies. In American studies, the protective effect of physical activity was lower (RR = 0.82, 95% CI: 0.75, 0.90) than in European studies (RR = 0.47, 95%CI: 0.33, 0.66). Forty-six per cent of the American studies reported on women, whereas among the European studies one-third reported on women. In order to exclude an effect of gender of the study population, we repeated our analyses with adjustment for this variable. Pooled relative risks did not meaningfully change and the difference between American and European studies remained (America: RR = 0.81, 95% CI: 0.71, 0.92, Europe: RR = 0.46, 95% CI: 0.33, 0.65).

Possibly, the American studies contain smaller contrasts between active and inactive groups than European ones. This

Table 3 Pooled relative risks from studies of occupational activity and the risk of stroke

	n	Relative risk (95% CI)	*P*-value for heterogeneity	I^2
A. Active—Inactive for studies that present risk estimates for more than 2 activity categories				
Total stroke	6	0.74 (0.49, 1.12)	0.01	66%
Haemorrhagic stroke	1	0.31 (0.13, 0.76)	—	—
Ischaemic stroke	5	0.57 (0.43, 0.77)	0.3	16%
B. Active—Moderately active for studies that present risk estimates for more than 2 activity categories				
Total stroke	6	0.92 (0.68, 1.24)	0.04	57%
Haemorrhagic stroke	1	3.36 (0.36, 31.57)	—	—
Ischaemic stroke	5	0.77 (0.60, 0.98)	0.5	—[a]
C. Moderately active—Inactive for studies that present risk estimates for more than 2 activity categories				
Total stroke	4	0.64 (0.48, 0.87)	0.9	—[a]
Haemorrhagic stroke	2	0.45 (0.14, 1.39)	0.6	—[a]
Ischaemic stroke	3	0.67 (0.35, 1.29)	0.7	—[a]
D. Physical activity dichotomized (studies that present risk estimates for dichotomized physical activity categories)				
Total stroke	6	0.87 (0.69, 1.09)	0.004	72%
Haemorrhagic stroke	2	0.58 (0.21, 1.58)	0.7	—[a]
Ischaemic stroke	2	1.00 (0.62, 1.63)	0.4	—[a]

[a] The I^2 statistic could not be calculated because the total variance was smaller than expected based on the within-study variance, e.g. studies included in this analysis were 'homogeneous'.

Table 4 Pooled relative risks from studies of leisure time activity and the risk of stroke

	n	Relative risk (95% CI)	*P*-value for heterogeneity	I^2
A. Active—Inactive for studies that present risk estimates for more than 2 activity categories				
Total stroke	19	0.78 (0.71, 0.85)	0.2	24%
Haemorrhagic stroke	9	0.74 (0.57, 0.96)	0.6	—[a]
Ischaemic stroke	11	0.79 (0.69, 0.91)	0.2	23%
B. Active—Moderately active for studies that present risk estimates for more than 2 activity categories				
Total stroke	4	0.95 (0.68, 1.32)	0.7	—[a]
Haemorrhagic stroke	0	—	—	—
Ischemic stroke	5	0.84 (0.63, 1.11)	0.9	—[a]
C. Moderately active—Inactive for studies that present risk estimates for more than 2 activity categories				
Total stroke	15	0.85 (0.78, 0.93)	0.5	—[a]
Haemorrhagic stroke	9	0.76 (0.55, 1.05)	0.9	—[a]
Ischaemic stroke	7	0.83 (0.64, 1.09)	0.04	55%
D. Physical activity dichotomized (studies that present risk estimates for dichotomized physical activity categories)				
Total stroke	8	0.92 (0.54, 1.58)	<0.001	78%
Haemorrhagic stroke	1	0.77 (0.00, 2.18)	—	—
Ischaemic stroke	1	0.83 (0.50, 1.43)	—	—

[a] The I^2 statistic could not be calculated because the total variance was smaller than expected based on the within-study variance, e.g. studies included in this analysis were 'homogeneous'.

lack of contrast might be due to a generally lower level of physical activity in the US compared with Europe. In surveys, the category most comparable between countries is the category of inactivity since it is generally defined as not being engaged in any or any meaningful physical activity. Data from the 1997–1998 National Health Interview Survey showed that in the US 38.3% of all adults never engaged in any light, moderate, or vigorous leisure time physical activity.[47] In The Netherlands only 12% of the population aged ⩾16 years is inactive.[48] This would mean that, especially in the US,

Table 5 Results from crude, weighted, and adjusted analyses on sources of heterogeneity[a]

		Crude analyses	Weighted analyses			
	n	RR[b] (95% CI)	RR (95% CI)[c]	RR[d]	RR[e]	RR[f]
Total stroke	16	0.79 (0.72, 0.86)	0.78 (0.76, 0.80)	0.78	0.79	0.77
Haemorrhagic stroke	8	0.75 (0.57, 1.00)	0.74 (0.69, 0.78)	0.74	0.74	0.72
Ischaemic stroke	8	0.82 (0.71, 0.96)	0.81 (0.78, 0.83)	0.80	0.81	0.80
			Adjusted analyses			
	n	*P*-value	RR (95% CI)			
Total stroke						
Cohort studies	16	—	—			
Male population	9	0.4	—			
US	13	0.008	0.82 (0.75, 0.90)			
Australia	0	—	—			
Asia	0	—	—			
Europe	3	0.008	0.47 (0.33, 0.66)			
Year of publication	16	0.8101	—			
Haemorrhagic stroke						
Cohort studies	6	0.9	—			
Male population	5	0.07	0.54 (0.36, 0.81)[g]			
US	4	0.2	—			
Australia	2	0.9	—			
Asia	2	0.1	—			
Europe	0	—	—			
Year of publication	8	0.14	—			
Ischaemic stroke						
Cohort studies	8	—	—			
Male population	4	0.2	—			
US	8	—	—			
Australia	0	—	—			
Asia	0	—	—			
Europe	0	—	—			
Year of publication	8	0.5	—			

[a] Restricted to stratum A of studies on leisure time physical activity and stroke risk excluding studies that did not report separate risk estimates for gender.
[b] Relative risk.
[c] Weighted for the total quality score.
[d] Weighted for the quality score for measuring physical activity.
[e] Weighted for the quality score for measuring disease status.
[f] Weighted for the quality score for epidemiological methodology.
[g] RR (95% CI) for female population: 0.76 (95% CI: 0.67, 0.86).

improving the level of physical activity is an important measure in preventing a disabling disease as stroke.

Recently, another meta-analysis on physical activity and stroke risk was published by Lee *et al*.[49] For the most part, our meta-analysis was based on the same studies. However, our research of the literature included four studies that were not identified by Lee *et al*.[9,28,35,39] Also, our meta-analysis included studies with dichotomous physical activity categories, whereas Lee *et al*. excluded these studies from their analysis. In the end, our meta-analysis included two more case-control and six additional cohort studies. The meta-analysis of Lee *et al*. included two studies that we excluded (one because it included physical fitness and one because of multiple publications).[6,50] Among cohort studies, Lee *et al*. calculated a pooled risk estimate for ischaemic stroke of 0.79 (95% CI: 0.69, 0.91) for high compared with low physical activity levels. For haemorrhagic stroke their pooled risk estimate was 0.66 (95% CI: 0.48, 0.91). When comparing moderate with low physical activity levels, they calculated risk estimates of 0.91 (95% CI: 0.80, 1.05) and 0.85 (95% CI: 0.64, 1.13) for ischaemic and haemorrhagic stroke respectively. In our meta-analysis, we found similar results and in case of ischaemic stroke the results were identical for high versus low physical activity levels (e.g. 0.79 [95% CI: 0.69, 0.91]). Lee *et al*. stratified for type of study

design, type of stroke, and reference and comparison categories. In the present meta-analysis, however, we further stratified for leisure time and occupational physical activity. Moreover, we explored several sources of heterogeneity, such as year of publication and country under study.

The present study summarized the results of various studies on the association between physical activity and stroke. An earlier meta-analysis by Berlin and Colditz addressed the association between physical activity and coronary heart disease.[1] They reported a pooled relative risk of 1.4 (95% CI: 1.0, 1.8) for coronary heart disease incidence and 1.9 (95% CI: 1.6, 2.2) for coronary heart disease mortality for sedentary occupations compared with high occupational activity.[1] In our meta-analysis, these comparison groups showed a pooled risk estimate of 1.4 (95% CI: 0.9, 2.0) for total stroke, 3.2 (95% CI: 1.3, 7.7) for haemorrhagic stroke, and 1.8 (95% CI: 1.3, 2.3) for ischaemic stroke. Therefore, the protective effect of occupational physical activity on the incidence of stroke seems to be at least comparable to and maybe even greater than the protective effect on coronary heart disease incidence. For leisure time physical activity, Berlin and Colditz reported pooled relative risks varying from 1.3 (95% CI: 1.0, 1.7) to 1.9 (95% CI: 1.0, 3.4) for coronary heart disease incidence and mortality.[1] In the present meta-analysis, low leisure time physical activity levels compared with high leisure time physical activity levels showed pooled risk estimates of 1.3 (95% CI: 1.2, 1.4) for total stroke, 1.4 (95% CI: 1.0, 1.8) for haemorrhagic stroke, and 1.3 (95% CI: 1.1, 1.4) for ischaemic stroke. Consequently, the protective effect of leisure time physical activity on the incidence of stroke seems to be comparable to the protective effect on coronary heart disease incidence.

If physical activity could be successfully increased at the population level, the public health impact is large. Firstly, because coronary heart disease and stroke, which are responsible for about 75% of all cardiovascular diseases, have been identified as the first and second causes of death worldwide.[51–53] Secondly, it has been predicted that annual mortality from non-communicable diseases such as coronary heart disease and stroke will increase from an estimated 28.1 million deaths in 1990 to 49.7 million deaths in 2020 and that coronary heart disease and stroke will remain the most important causes of death in the years to come.[54] Thirdly, these diseases are relatively expensive to the health care system. In The Netherlands for example, it has been estimated that the costs of coronary heart disease and stroke are 0.9 and 1.0 billion Euro respectively and that these diseases are responsible for approximately 5.5% of all health care costs in The Netherlands.[55]

In conclusion, this meta-analysis provides quantitative evidence that physical activity is an important modifiable risk factor for stroke. Compared with inactivity, the largest risk reduction is obtained for moderately intense physical activity. The protective effect of physical activity on the incidence of stroke needs more emphasis in the prevention of this important public health problem.

KEY MESSAGES

- Physical activity is an important modifiable risk factor in preventing stroke.
- Compared with inactivity, the largest risk reduction is obtained for moderately intense physical activity.
- Country under study and possibly gender are sources of heterogeneity among studies on physical activity and stroke.

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Appendix Scoring list to assess study quality adapted from Powell *et al.*[2]

	No, or uncertain (0 points)	Partly present (1 point)	Yes (2 points)
Measurement of physical activity			
1. The operational definition of physical activity should be stated and understandable			
2. The reliability and validity of the measurement instrument should be determined			
3. The activity measure should be based on the activities reported specifically for each participant rather than on presumed activities based on membership in a group			
4. The measure should include information about the frequency, duration, and intensity of the activities encompassed			
5. The level of physical activity during earlier periods of life should be determined			
6. For cohort studies, adherence to the original physical activity classification should be determined			
7. The information about the physical activity measure should be systematically collected with specified standard methods.			
Measurement of stroke			
1. The criteria for the diagnosis of stroke should be clearly specified and applied consistently throughout the study.			
2. The information about the diagnosis of stroke should be systematically collected by using specified, standard sources and methods			
3. The diagnosis should be made separately for ischaemic and haemorrhagic stroke			
4. The identification of persons with stroke should be independent of their activity status			
Epidemiological methods			
1. The physical activity status should be determined for a period that precedes the onset of stroke			
2. Analyses should be adjusted for age, sex, blood pressure, cardiovascular diseases, diabetes, smoking status and alcohol consumption			
3. For cohort studies, the original group of participants should be typical of the population from which they are drawn			
For case-control studies, both cases and controls should come from the same population			
4. For cohort studies, few participants should be lost to follow-up, or it should be established that the original activity status is similar for those who are lost and those who remain			
5. For case-control studies, cases and controls should be chosen and the data collected according to a predetermined protocol			
6. For case-control studies, both data collectors and respondents should be unaware of the hypothesis under consideration			
7. For case-control studies, any constraint should apply equally to cases and controls			